



Original Research

Association between primary origin (head, body and tail) of metastasised pancreatic ductal adenocarcinoma and oncologic outcome: A population-based analysis



Tara M. Mackay^{a,*,1}, Felice N. van Erning^{b,1},
Lydia G.M. van der Geest^b, Jan Willem B. de Groot^c,
Nadia Haj Mohammad^d, Valery E. Lemmens^{b,e},
Hanneke W. van Laarhoven^f, Marc G. Besselink^a,
Johanna W. Wilmink^{f,*}, for the Dutch Pancreatic Cancer Group

^a Department of Surgery, Cancer Center Amsterdam, Amsterdam UMC, University of Amsterdam, the Netherlands

^b Department of Research, Netherlands Comprehensive Cancer Organisation (IKNL), Utrecht, the Netherlands

^c Department of Medical Oncology, Oncology Center Isala, Zwolle, the Netherlands

^d Department of Medical Oncology, University Medical Center, Utrecht University, the Netherlands

^e Department of Public Health, Erasmus Medical Center, Rotterdam, the Netherlands

^f Department of Medical Oncology, Cancer Center Amsterdam, Amsterdam UMC, University of Amsterdam, the Netherlands

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Abstract Introduction: The relation between the primary origin of metastasised pancreatic ductal adenocarcinoma (PDAC)—head, body or tail—metastatic patterns and outcomes has not yet been investigated in large population-based studies.

Methods: Patients with metastasised PDAC at diagnosis from the Netherlands Cancer Registry were included (2005–2015). We compared number of metastatic organ sites (1, 2, ≥ 3) and specific metastatic organ sites (peritoneum, liver, lung and extra-regional lymph nodes) for the different primary tumour locations. Cox regression analyses were used to determine the association of tumour location and metastatic organ site(s) with overall survival.

Results: Overall, we included 9952 patients with metastasised PDAC. The primary origin was head in 5644 (57%), body in 1671 (17%) and tail in 2637 (26%) patients. Differences between

* Corresponding author: Dept. of Medical Oncology, G4-212, Cancer Center Amsterdam, Amsterdam UMC, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands. Fax: +31 20 6919743.

** Corresponding author: Dept. of Surgery, G4-134, Cancer Center Amsterdam, Amsterdam UMC, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands. Fax: +31 20 5666659.

E-mail addresses: t.m.mackay@amc.nl (T.M. Mackay), j.w.wilmink@amc.uva.nl (J.W. Wilmink).

¹ Shared first author.

primary origins were the number of metastatic organ sites (proportions ≥ 3 sites for head: 4%, for body: 8% and for tail: 13%, $p < 0.0001$) and peritoneal metastases (present in 13% for head, 24% for body and 30% for tail; $p < 0.0001$). Median overall survival was 2.6 months for head PDAC (reference), 2.4 months for body PDAC (HR 1.02 [0.97–1.08]) and 1.9 months for tail PDAC (HR 1.20 [1.15–1.26]). Of patients with one metastatic organ site, the worst survival compared with other sites was seen with liver only metastases (2.5 months vs. 2.7–5.1 months), and the best survival for patients, with extra-regional lymph node only metastases (5.1 months).

Conclusion: Metastatic patterns differ among the primary origins for PDAC with metastasised tail tumours having more metastatic sites, more often peritoneal metastases and worse survival.

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1. Introduction

Survival of patients with metastatic pancreatic ductal adenocarcinoma (PDAC) is notoriously poor. A recent Dutch population-based study (2007–2011) found a median overall survival (OS) of 10 weeks [1]. In the past years, new palliative chemotherapy strategies (i.e. gemcitabine + nab-paclitaxel and folinic acid-fluorouracil-irinotecan-oxaliplatin [FOLFIRINOX]) have improved the median OS to 6–11 months [2–5]. Most studies report worse survival for patients with metastatic body or tail compared with head PDAC [6–9].

Primary body and tail PDAC are generally larger and more often metastasised at diagnosis than head tumours, possibly because of delayed presentation due to absence of specific symptoms [6,10–12]. Besides, location of resected PDAC in the body and tail was associated with the molecular squamous subtype and more aggressive tumour biology than resected head PDACs [7]. This may be an underlying cause for worse clinical outcomes of patients with pancreatic body and tail cancer, also within the metastatic patient subgroup.

Common sites of PDAC metastases are the liver, lung, peritoneum and distant lymph nodes [13,14]. Patients with multiple metastatic sites and liver and/or peritoneal metastases have worse OS than patients with a single metastatic site or other metastatic locations [15–18]. Previous studies, however, did not investigate the relation between primary tumour location, metastatic patterns and survival, specifically within the metastatic PDAC subgroup only. It is important to investigate survival in relation to metastatic pattern per primary tumour origin as some smaller non-randomized studies suggest that local ablative or surgical therapy may be beneficial for a selected group of patients with favourable outcomes [19,20]. Therefore, the aim of this study is to investigate if metastatic patterns differ among the origins of PDAC and if these differences explain the survival difference in a population-based cohort of patients with metastatic pancreatic cancer at primary diagnosis (2005–2015) from the Netherlands Cancer Registry (NCR).

2. Materials and methods

2.1. Data collection

This is a retrospective study using data from the nationwide NCR. The NCR is a population-based registry which collects data on all newly diagnosed cancer patients in the Netherlands (about 17 million inhabitants). Information on patient and tumour characteristics, diagnosis and treatment is routinely extracted from the medical records by trained administrators of the NCR. Anatomical sites of the primary tumour and metastases are registered as per the International Classification of Disease—Oncology (ICD-O-3). The TNM (tumour-node-metastasis) classification is used for stage notification of the primary tumour, based on the edition valid at time of cancer diagnosis. Survival data is obtained by annual linkage with the Municipal Personal Records Database, which contains information on the vital status of all Dutch inhabitants. This study was designed in accordance with the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines.

2.2. Study population

For the present study, we selected all patients with PDAC or suspected PDAC (ICD-O C25, morphology codes 8010, 8012, 8020, 8140, 8141, 8260, 8310, 8440, 8480, 8481, 8490, 8500 and 8560 or a non-microscopic verified invasive neoplasm of the pancreas suspected for adenocarcinoma [i.e. no cytological or histological verification]) diagnosed in the Netherlands between 2005 and 2015. Primary diagnosis (clinical TNM staging) was made with imaging studies or surgical exploration. Patients younger than 18 years at diagnosis or residing abroad and patients diagnosed at autopsy were excluded. Patients were classified based on the tumour location: head (C25.0), body (C25.1), tail (C25.2) and others (C25.3–9). We excluded the latter group (C25.3–9). Furthermore, we excluded all patients without distant metastases and with distant metastases who underwent resection.

2.3. Statistical analyses

Descriptive statistics were used to compare patient, tumour, metastasis and treatment characteristics among primary tumour locations. Characteristics included sex, age (categorized as <65, 65–74 and ≥ 75 years), microscopic verification, primary tumour size (only available in 2015; categorized as: 0–2, >2–4, >4 cm and unknown), number of metastatic organ sites (categorized as 1, 2, ≥ 3 or unknown), specific metastatic organ sites (categorized as peritoneum, liver, lung, extra-regional lymph nodes and other), surgical exploration (available for 2009–2015) and chemotherapy.

We used univariable and multivariable Cox regression analyses to determine the association of tumour location and metastatic organ site(s) with OS, and the results are presented as hazard ratios (HRs) with 95% confidence interval (CI). The variables used in the multivariable analyses, besides primary tumour location and metastatic organ site(s), were gender, age, period of diagnosis and chemotherapy. Metastatic organ site(s) was categorized as liver only, peritoneum only, lung only, extra-regional lymph nodes only, other site only, two sites (any combination), ≥ 3 sites (any combination) and unknown. For the most common metastatic organ site(s), i.e. liver only, peritoneum only, 2 sites and ≥ 3 sites, one-year OS as per the tumour location was analysed by means of Kaplan-Meier curves and was compared with Log-Rank tests. We defined survival time as the time between the date of diagnosis and date of death or censoring (February 1, 2018). Sensitivity

analysis was performed including only patients with pathologically confirmed PDAC.

P values below 0.05 were considered statistically significant. We used SAS/STAT® statistical software (SAS system 9.4; SAS Institute, Cary, NY) for all analyses.

3. Results

Overall, 9952 patients with metastasised PDAC were included (Fig. 1). Primary origin was the pancreatic head in 5644 (57%) patients, the body in 1671 (17%) patients and the tail in 2637 (26%) patients.

Table 1 provides an overview of the patient, tumour and treatment characteristics by primary origin. We particularly found large differences for tumour size (i.e. proportion tumour size >4 cm in the head: 26%, body: 41% and tail: 52%, $p < 0.0001$) and metastasis found at surgical exploration (11% in head, 2% in body and 3% in tail, $p < 0.0001$).

Fig. 2 shows that the number of metastatic organ sites differs by primary origin of PDAC ($p < 0.0001$). Multiple metastatic sites were found most often in patients with tail tumours. A specification of the affected metastatic organ sites per primary tumour location is presented in Fig. 3. Differences were especially present with regard to peritoneal metastases ($p < 0.0001$), but differences were also present for liver ($p = 0.0035$), lung ($p < 0.0001$) and other metastases ($p < 0.0001$). There was no difference in the proportion of extra-regional lymph nodes among primary tumour locations ($p = 0.726$).

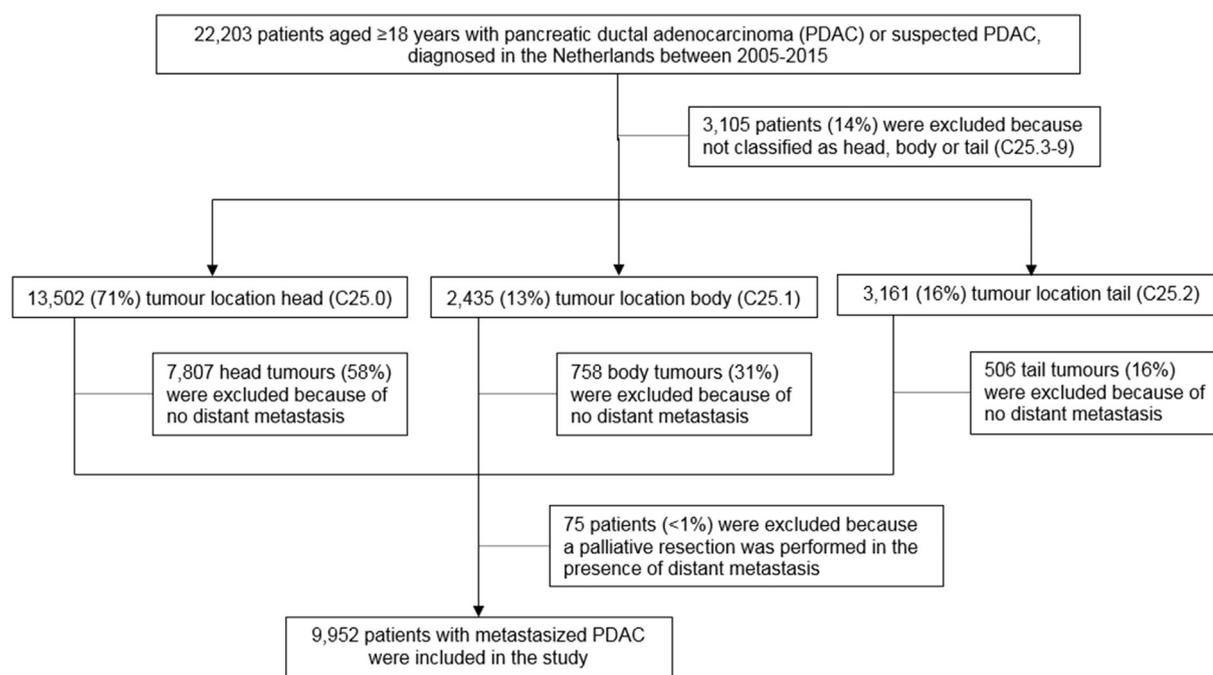


Fig. 1. Selection of the study population.

Table 1

Patient, tumour and treatment characteristics by the tumour location of 9952 patients with metastasised pancreatic ductal adenocarcinoma.

| Characteristics | Head n (%) | Body n (%) | Tail n (%) | P-value ^a |
|----------------------------------|------------|------------|------------|----------------------|
| Total n | 5644 | 1671 | 2637 | |
| Sex | | | | |
| Male | 2912 (52) | 802 (48) | 1475 (56) | <0.0001 |
| Female | 2732 (48) | 869 (52) | 1162 (44) | |
| Age | | | | |
| <65 years | 1874 (33) | 573 (34) | 906 (34) | 0.0006 |
| 65–74 years | 1868 (33) | 578 (35) | 964 (37) | |
| ≥75 years | 1902 (34) | 520 (31) | 767 (29) | |
| Microscopically verified | | | | |
| Yes | 3710 (66) | 1207 (72) | 1994 (76) | <0.0001 |
| No | 1934 (34) | 464 (28) | 643 (24) | |
| Tumour size (2015 only) | | | | |
| 0–2 cm | 44 (8) | 18 (9) | 5 (2) | <0.0001 |
| >2–4 cm | 243 (46) | 65 (31) | 72 (25) | |
| >4 cm | 135 (26) | 85 (41) | 153 (52) | |
| Unknown | 104 (20) | 39 (19) | 62 (21) | |
| Surgical exploration (2009–2015) | | | | |
| Yes | 419 (11) | 29 (2) | 52 (3) | <0.0001 |
| No | 3347 (89) | 1191 (98) | 1878 (97) | |
| Chemotherapy | | | | |
| Yes | 1252 (22) | 502 (30) | 729 (28) | <0.0001 |
| No | 4392 (78) | 1169 (70) | 1908 (72) | |

^a P-value indicates significance of the Chi-square test.

The most common metastatic organ site(s) were liver only (n = 5007; 50.3%), peritoneum only (n = 770; 7.7%), two metastatic organ sites (n = 2171; 21.8%) and ≥three metastatic organ sites (n = 867; 8.7%, Table 2).

As presented in Table 2, chemotherapy was given to 22%, 30% and 28% of patients with head, body and tail PDAC, respectively (p < 0.0001). Median OS was worst for tail PDAC with 1.9 months compared with that of 2.6 and 2.4 months for head and body PDAC, respectively. This difference remained after adjustment for metastatic site(s) with worse survival for tail than for head cancer in all analyses (adjusted HR, 1.23; 95% CI, 1.17–1.29) and for body than head cancer only after additional adjustment for treatment with chemotherapy (adjusted HR, 1.13; 95% CI, 1.06–1.19). In patients treated with

chemotherapy, median OS was 6.4 months for head, 5.8 months for body and 5.0 months for tail tumours. Patients with two or ≥three metastatic organ sites had the worst survival, independent of the origin of the primary tumour. Of patients with one metastatic organ site, liver only had the worst survival compared with other sites (Fig. 4).

Sensitivity analysis including only patients with pathologically confirmed PDAC showed slightly better survival but overall similar trends (data not shown).

For patients with liver metastases only, one-year OS for the head, body and tail was 6.5%, 6.8% and 5.6%, and median OS was 2.5, 2.6 and 2.1 months, respectively (p = 0.004). For peritoneal metastasis only, these were 13.9%, 11.8% and 10.5%, and 3.4, 2.3 and 2.2 months,

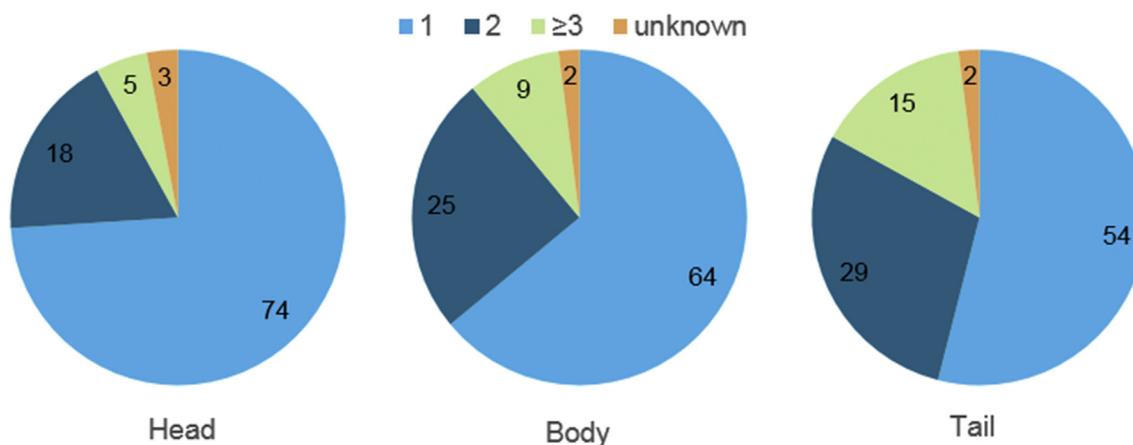


Fig. 2. Proportional distribution of the number of metastatic organ sites by primary tumour location.

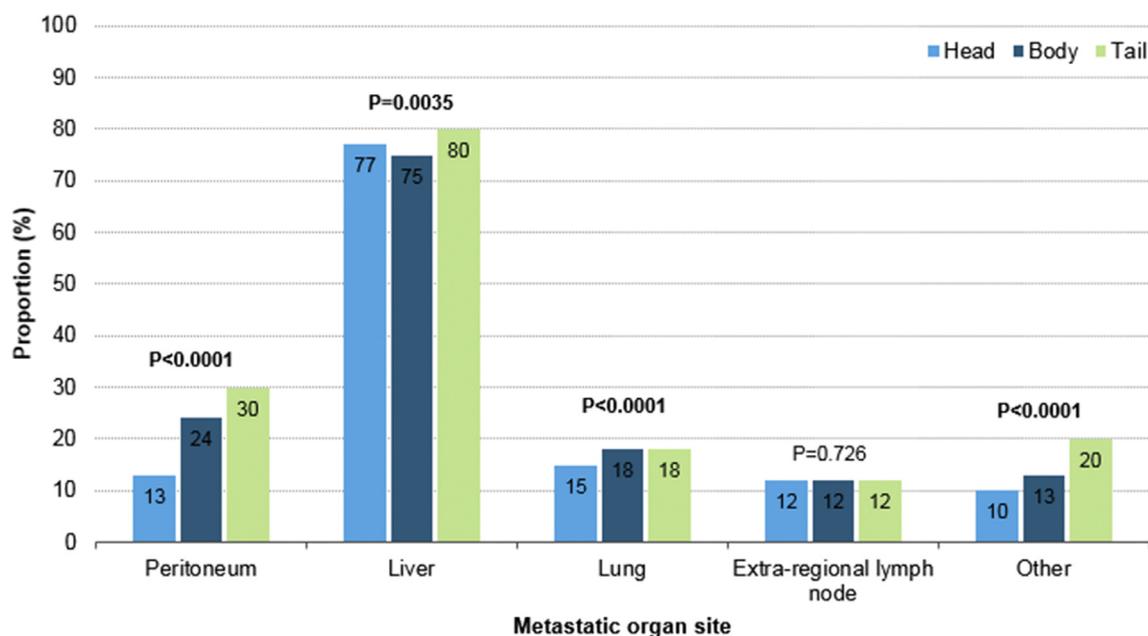


Fig. 3. Metastatic organ sites by the primary tumour location. Patients with an unknown number and specification of metastatic organ sites excluded. Bold P-values indicate statistical significance.

respectively. ($p = 0.051$). For two metastatic organ sites, these were 5.8%, 6.0% and 5.4%, and 2.0, 2.0 and 1.8 months, respectively ($p = 0.245$). For three or more metastatic sites these were 3.0%, 3.9% and 1.9%, and 1.2, 1.5 and 1.3 months, respectively ($p = 0.028$).

4. Discussion

This is the first large population-based study that investigated the relation between the primary origin of metastasised PDAC and metastatic patterns on

the oncologic outcome. Patients with metastasised PDAC originating from the pancreatic tail had more metastatic sites, more often peritoneal metastases and worse survival than patients with head or body PDAC.

Previous studies found worse outcomes for patients with metastatic body and tail tumours than for patients with head PDAC [6–9]. Only few studies reported on body and tail PDAC separately, and metastatic patterns are largely unknown [9]. Our study showed that metastatic patterns differed significantly among the primary origins of PDAC. Especially, patients with tail tumours have multiple metastatic organ sites and more often

Table 2

Survival analyses of 9952 patients with metastasised pancreatic ductal adenocarcinoma ($n = 9952$).

| Characteristics | Total n | Chemotherapy (%) | Median OS (months) | Unadjusted HR (95% CI) | Adjusted HR (95% CI) without chemotherapy ^a | Adjusted HR (95% CI) with chemotherapy ^b |
|---------------------------------|---------|------------------|--------------------|-------------------------|--|---|
| Tumour location | | | | | | |
| Head | 5644 | 22 | 2.6 | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| Body | 1671 | 30 | 2.4 | 1.02 (0.97–1.08) | 1.03 (0.97–1.09) | 1.13 (1.06–1.19) |
| Tail | 2637 | 28 | 1.9 | 1.20 (1.15–1.26) | 1.14 (1.09–1.19) | 1.23 (1.17–1.29) |
| Metastatic organ site(s) | | | | | | |
| Liver only | 5007 | 26 | 2.5 | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| Peritoneum only | 770 | 26 | 2.7 | 0.85 (0.78–0.91) | 0.84 (0.78–0.91) | 0.82 (0.76–0.89) |
| Lung only | 376 | 24 | 4.7 | 0.65 (0.59–0.72) | 0.61 (0.55–0.67) | 0.57 (0.51–0.63) |
| Extra-regional lymph nodes only | 308 | 27 | 5.1 | 0.58 (0.52–0.66) | 0.58 (0.52–0.65) | 0.56 (0.50–0.63) |
| Other site only | 206 | 18 | 3.5 | 0.74 (0.65–0.86) | 0.71 (0.62–0.81) | 0.64 (0.55–0.73) |
| 2 sites (any combination) | 2171 | 25 | 1.9 | 1.16 (1.10–1.22) | 1.16 (1.10–1.22) | 1.17 (1.11–1.23) |
| ≥3 sites (any combination) | 867 | 24 | 1.3 | 1.56 (1.45–1.68) | 1.61 (1.50–1.73) | 1.69 (1.57–1.82) |
| Unknown | 247 | 12 | 2.3 | 1.10 (0.97–1.26) | 1.00 (0.88–1.14) | 0.90 (0.79–1.03) |

OS, overall survival; CI, confidence interval; HR, hazard ratio

Bold numbers indicate statistical significance.

^a Besides adjustment for tumour location and metastatic site(s), hazard ratios also adjusted for gender, age and period of diagnosis.

^b Besides adjustment for tumour location and metastatic site(s), hazard ratios also adjusted for gender, age, period of diagnosis and chemotherapy.

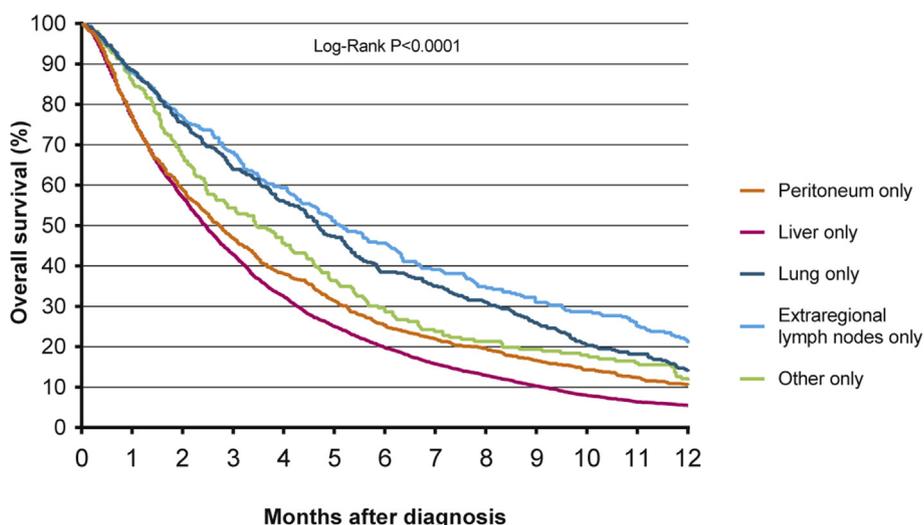


Fig. 4. Overall survival per metastatic organ site only.

peritoneal metastases than head and body tumours. This could be explained by the late onset of symptoms of tail tumours leading to more extensive metastases at the time of diagnosis [11,21].

Concurrent with the metastatic pattern differences, median OS decreased from 2.6 to 2.4 to 1.9 months for head, body and tail tumours, respectively. In all analyses, tail PDAC had the worst survival compared with head and body PDAC. This is partly explained by the fact that tail tumours metastasise to the liver, peritoneum and multiple sites more often than head or body tumours. Previous studies indeed reported worse outcomes for patients with similar metastatic patterns to the liver, peritoneum or multiple sites [13,15–18]. However, after adjustment for baseline characteristics, tumour location and metastatic site(s), patients with primary PDAC location tail still have worse survival than head and body locations. This suggests that metastatic patterns are not the sole explanation for the survival difference among the various PDAC origins. Tail tumours are not only diagnosed later but they also appear to have a more aggressive tumour biology which could explain our findings [7]. In addition, as metastatic PDAC in the head is more often diagnosed at surgical exploration, these patients are diagnosed at an earlier time stage, leading to a lead time bias and an artificial longer survival period. However, as the proportion of patients undergoing surgical exploration is limited, this is not expected to fully explain the differences in survival. Furthermore, recovery from futile surgery and stent placement for bile duct obstruction may have precluded the administration of chemotherapy, because chemotherapy use was lowest in patients with head PDAC.

In the literature, median OS of patients treated with chemotherapy ranges from 4.4 to 11.1 months for different chemotherapy regimens, including the newer FOLFIRINOX and nab-paclitaxel and gemcitabine

regimen [3–5,14,22,23]. Median OS after chemotherapy in our cohort (5.0–6.4 months) falls within the lower range of these previous studies. This is explained by two reasons; first, outcomes from population-based data are not comparable with outcomes of patients treated in randomized clinical trials (RCTs) as strict inclusion criteria in RCTs select patients with good performance status and consequently higher survival rates. Second, the years of publication of RCTs with FOLFIRINOX and gemcitabine + nab-paclitaxel were in 2011 and 2013, respectively. Because of the inclusion period of this study (2005–2015), the majority of patients in our study were probably treated with gemcitabine monotherapy. Details about chemotherapy use are not available for the current time period.

There were some limitations to this study. Overall, 14% of patients were excluded because tumours could not be classified as head, body or tail. It is suspected that these tumours had overlap between locations (e.g. head-body or body-tail). Furthermore, no data on comorbidity are available in the NCR, whereas comorbidity will have influenced treatment decisions. As tumour size was only available in the NCR in 2015 and the proportion of patients with ‘unknown’ size was relatively high (20%), adjustment for tumour size and sensitivity analysis including 2015 data only were not possible. In addition, only the number of metastatic sites, but not the number of metastases per metastatic site (total tumour burden) was available for our study. Finally, there may be a small overestimation of survival in this study as Fest *et al.* suggested an underestimation of pancreatic cancer incidence of elderly patients with poorer survival that were registered in the NCR [24].

5. Conclusion

Metastatic patterns differ among the primary origins (head, body and tail) of metastatic PDAC, with the

worst outcome for patients with tail PDAC. The differences in metastatic patterns do not fully explain the difference in OS among patients with head, body and tail primary tumour locations and suggest that other causes, such as more aggressive tumour biology or the extensiveness of the metastatic disease at diagnosis of tail origin, could be of influence.

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Conflict of interest statement

None declared.

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